ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2018, **54**, 515

Received 21st November 2017,
Accepted 13th December 2017

DOI: 10.1039/c7cc08897c

rsc.li/chemcomm

Radical-mediated intramolecular β-C(sp^3)–H amidation of alkylimidates: facile synthesis of 1,2-amino alcohols†

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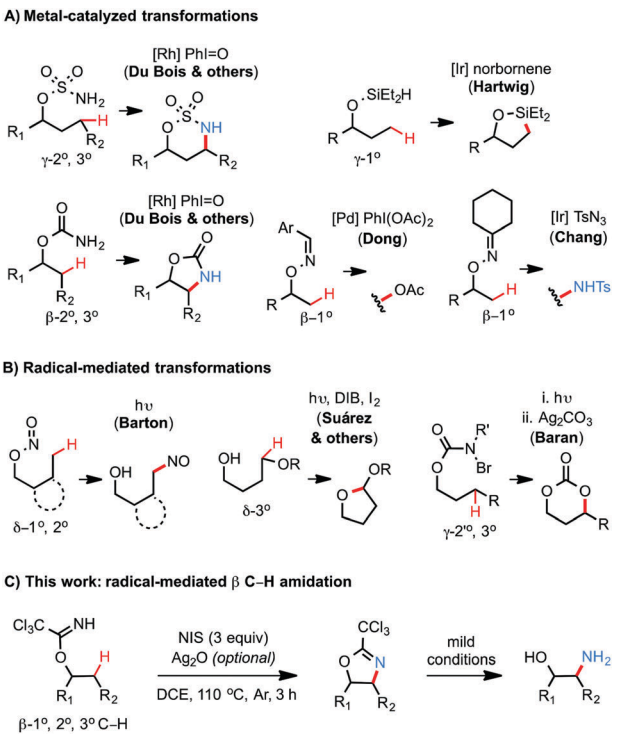
A new radical-mediated intramolecular β-C(sp^3)–H amidation reaction of *O*-alkyl trichloro- or arylimidates is reported. Various oxazolines were efficiently prepared from easily accessible alcohol starting materials. The trichloro-oxazoline products can be hydrolyzed under mild conditions to give valuable 1,2-amino alcohols. This amidation reaction exhibits a broad substrate scope and good functional group tolerance, and offers a powerful means for the C(sp^3)–H functionalization of alcohols. Mechanistic studies suggest that a sequence of 1,5-HAT of an imidate radical, iodination and cyclization might be operative.

Selective and efficient functionalization of C(sp^3)–H bonds of alcohols could potentially streamline the synthesis of complex molecules and enable late-stage modifications. However, due to the relatively weak metal-binding ability of oxygen, metal-catalyzed directed C(sp^3)–H functionalization reactions of alcohols and their derivatives are much more challenging than carbonyl and amine compounds, which often require sophisticated substrate designs and proceed with a narrow transformation scope (Scheme 1A).[1–4] Radical-mediated reactions under photochemical conditions, such as the Barton nitrile ester reaction[5] and Suárez intramolecular alkoxylation[6] reactions, are well examined C(sp^3)–H functionalizations of alcohols. However, their relatively narrow substrate scope has hampered broad applications. Recently, Baran reported an elegant modification of the Hofmann–Löffler–Freytag (HLF)[7–9] reaction for the C(sp^3)–H bromination of carbamate derivatives of alcohols to synthesize 1,3-diols.[10] Despite recent advances, more synthetically useful and broadly applicable methods for radical C(sp^3)–H functionalization of alcohols are in great demand. Herein, we report a simple protocol for a radical-mediated β-selective intramolecular C(sp^3)–H amidation reaction of imidate derivatives of alcohols, generating oxazolines.[11–16] The resulting oxazolines can be hydrolyzed under mild conditions, affording various 1,2-amino alcohols.[17]



Scheme 1 Strategies for the C(sp^3)–H functionalization of alcohol and derivatives.

We attempted the C–H functionalization of *O*-octyl trichloroacetimidate **1** under various conditions (Table 1).[18] **1** was prepared from octanol and trichloroacetonitrile in excellent yield. Reaction of **1** using a $Pd(OAc)_2$ catalyst and a phenyliodonium diacetate (PIDA) oxidant did not afford the initially expected imidate-directed β-C–H acetoxylated product (entry 1). However, the reaction with $Pd(OAc)_2$ and 2 equiv. of *N*-iodosuccinimide (NIS) in toluene gave the cyclized oxazoline **2** in

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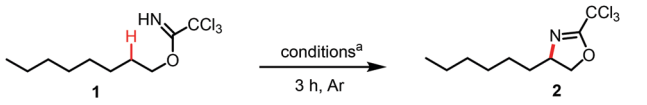
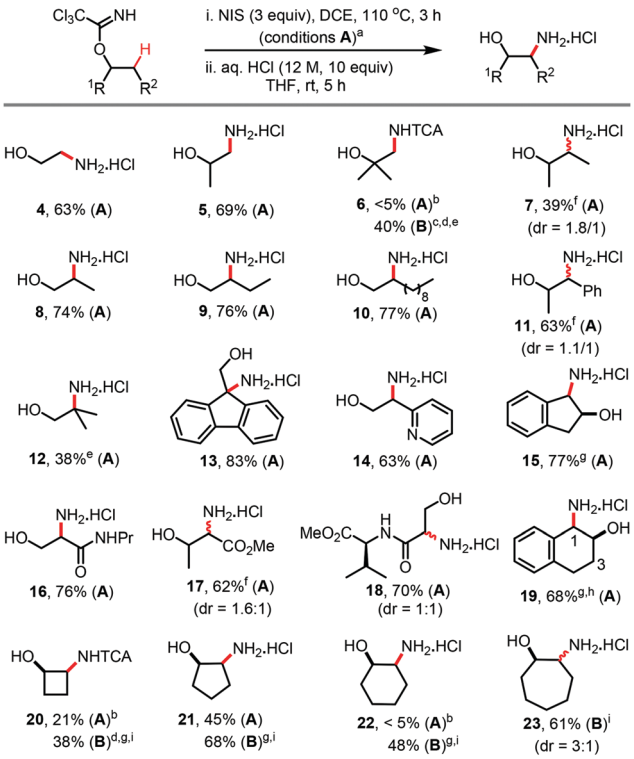
† Electronic supplementary information (ESI) available. CCDC 1561816 and 1561818. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7cc08897c

Table 1 Intramolecular β-C–H amination of **1**



Entry	Reagents (equiv.), temp.	Solvents	Yield of 2[b] (%)
1	$Pd(OAc)_2$ (0.1), $PhI(OAc)_2$ (2), 100 °C	Toluene	ND
2	$Pd(OAc)_2$ (0.1), NIS (2), 100 °C	Toluene	37
3	NIS (2), 100 °C	Toluene	56
4	$PhI(OAc)_2$ (2), I_2 (0.2), 100 °C	Toluene	46
5	$PhI(OAc)_2$ (2), 100 °C	Toluene	ND
6	I_2 (2), 100 °C	Toluene	ND
7	NIS (2), 110 °C	Toluene	54
8	NIS (2), 110 °C	DCE	70
9	NIS (3), 110 °C	Toluene	68
10	NIS (3), 110 °C	CH_3CN	41
11	**NIS (3), 110 °C**	**DCE**	**86 (74)[c]**
12	NIS (3), 110 °C, in the dark	DCE	81
13	NIS (3), 110 °C, air	DCE	65
14	NIS (3), Ag_2O (1.5), 110 °C	DCE	85
15	NIS (3), Cs_2CO_3 (2), 110 °C	DCE	85
16	NCS (3), 110 °C	DCE	ND
17	NBS (3), 110 °C	DCE	<5

[a] All reactions were conducted on a 0.2 mmol scale at 0.2 M concentration. [b] ^{1}H-NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield of **3** after acidic treatment. See the ESI for more experimental conditions.



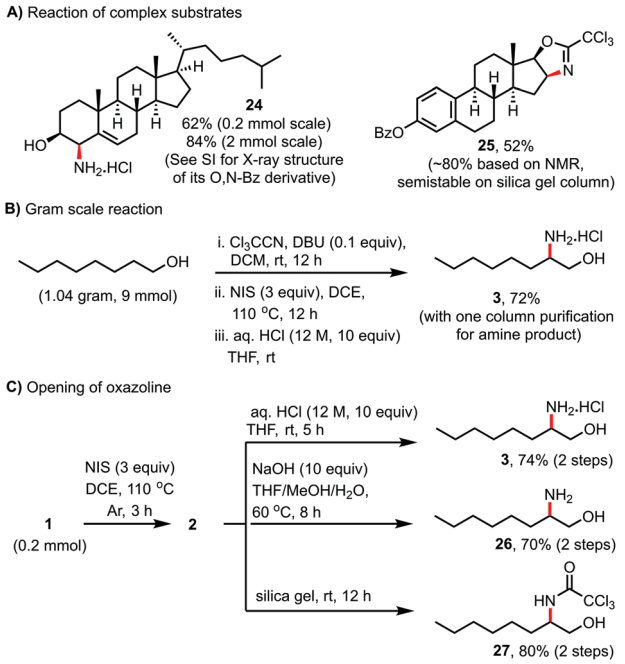
Scheme 2 β-C(sp^3)–H amination of *O*-alkyl trichloroacetimidate. (a) Isolated yield over 2 steps on a 0.2 mmol scale. Conditions **B** are similar to conditions **A** except for the addition of 1.5 equiv. of Ag_2O (see entry 14, Table 1). (b) >90% conversion of SM; a complex mixture of products was formed. (c) 60 °C, 1 h. (d) Partially hydrolyzed trichloroacetimide (TCA) products were obtained after the treatment with silica gel (see Scheme 3C). (e) The amidation reactions proceeded with full conversion and produced few side products. (f) No products of methyl C–H amination were observed. (g) Only a *cis*-aminated product was observed. (h) No C_3-aminated product was observed. (i) Two unidentified minor products (<10%) were observed for the initial amidation step. Their NMR and MS spectra do not match those of any iodinated or eliminated intermediates.

37% yield (entry 2). Interestingly, the cyclization reaction afforded a higher yield (56%) in the absence of Pd catalyst (entry 3). Similarly, the reaction with PIDA and I_2 gave **2** in 46% yield (entry 4–6). Following optimization, 3 equiv. of NIS in 1,2-dichloroethane (DCE) at 110 °C under Ar gave **2** in 86% yield (based on NMR). **2** is semi-stable to silica gel flash chromatography; the hydrolyzed product 2-amino-1-octanol **3** (see Scheme 3B) was obtained in 74% isolated yield after treatment with 10 equiv. of aq. HCl in THF at room temperature (rt).

Regarding the optimization, we note: (1) the cyclization proceeded well with or without light (entry 12); (2) the reaction yield diminished (65%) when carried out in air (entry 13); (3) substituting NCS or NBS under the same conditions gave little desired product **2** (entries 17, 18).

With the optimized conditions **A** (see entry 11, Table 1) in hand, we investigated the substrate scope of this NIS-mediated intramolecular β-C(sp^3)–H amidation reaction (Scheme 2). In general, these reactions proceeded cleanly, generating only a very small amount of hydrolyzed or O-to-N rearranged byproducts (<10%). We suspect that the isolated yield of some of our amine products was diminished upon evaporation of low molecular weight oxazoline intermediates during the workup of the amidation step (see **6**, **7**, **12**). As exemplified by **4–6**, trichloroacetimidates of primary, secondary and tertiary alcohols are compatible, and form the corresponding 2-amino alcohols after hydrolysis treatment. We were pleased to find that the amidation of β methyl groups proceeded well despite the relatively weak reactivity of primary C–H bonds in radical reactions (see **4**, **5**). As shown in **8–10**, the amidation of unactivated methylene C–H bonds afforded a slightly higher yield than for unactivated methyl C–H bonds. Substrates bearing both β methyl and methylene groups underwent reaction exclusively at the methylene position (see **7**, **11**, **17**). Functionalization of benzylic C–H bonds also proceeded well (see **15**, **19**). The reactions at the α-methylene group of esters and amides gave α-amino acid products in good yield (see **16–18**). A pyridine group was tolerated (see **14**). As shown in **15** and **19**, the amidation of benzylic methylene C–H bonds of cyclic substrates proceeded with good yields and exclusive *cis*-diastereoselectivities. In comparison, the reactions of the trichloroimidates of cyclobutanol, cyclopentanol and cyclohexanol resulted in a poor yield under conditions **A** (**20–22**). However, the yields were improved by the addition of 1.5 equiv. of Ag_2O (conditions **B**, entry 14 of Table 1).

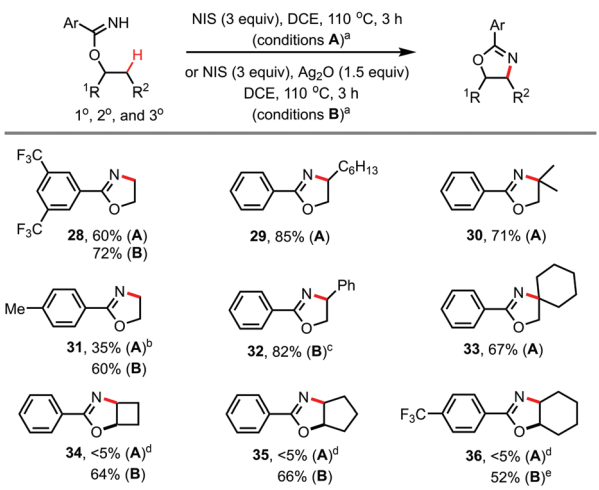
As shown in Scheme 3A, this β-C(sp^3)–H amidation reaction was applied for the modification of complex substrates. The aminated derivative of cholesterol **24** and the oxazoline derivative of estradiol **25** were obtained in good yields and with excellent regio- and *cis*-diastereoselectivities. As shown in Scheme 3B, 2-amino-1-octanol **3** was obtained in 72% overall yield from 1-octanol in three steps using only one chromatographic purification on a one gram scale. In addition to acidic



Scheme 3 Synthetic application of β-C–H amination reactions. Isolated yield on a 0.2 mmol scale under standard conditions **A** unless specified.

hydrolysis with aq. HCl in THF, treatment of oxazoline **2** with 10 equiv. of NaOH in THF/MeOH/H_2O at 60 °C gave the free amino alcohol **26** in excellent yield (Scheme 3C). Moreover, the treatment of **2** with silica gel at rt selectively gave partially hydrolyzed trichloroacetimide **27**.

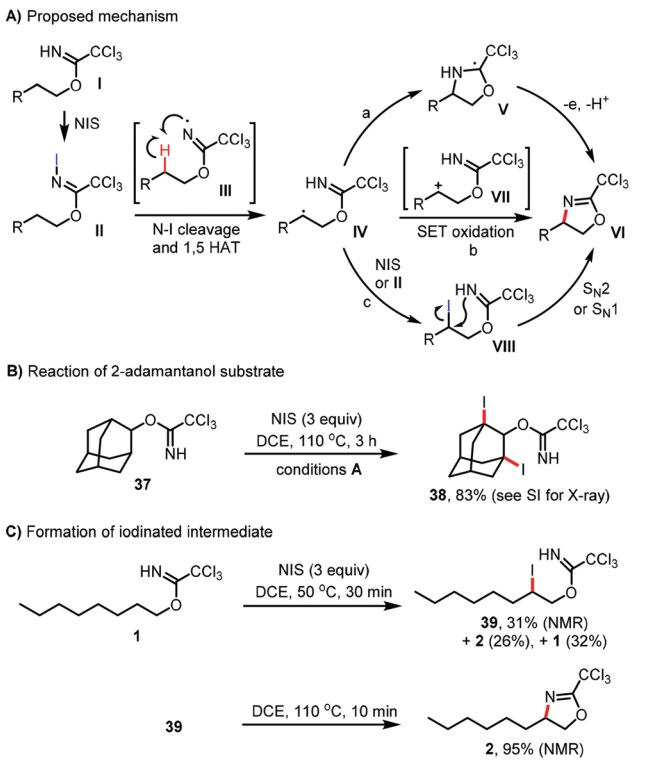
As seen in Scheme 4, β-C(sp^3)–H amination reactions of various arylimidates proceeded well under standard conditions **A** or **B**, giving the corresponding 2-aryloxazolines in a good to excellent yield. 2-Aryloxazolines are more stable than 2-trichloro-oxazolines and can be purified by silica gel chromatography.



Scheme 4 β-C(sp^3)–H amination of benzimidates. (a) Isolated yield on 0.2 mmol scale at 0.2 M concentration. (b) ~70% conversion of SM. (c) NIS (1.2 equiv.) and Ag_2O (0.6 equiv.). (d) A complex mixture of products was formed. (e) **34** is semi-stable to silica gel chromatography, ~80% yield based on NMR.

As seen in **28–30**, the amidation reactions of primary, secondary and tertiary C(sp^3)–H bonds afforded good yields. As exemplified by **28** and **31**, arylimidates with electron withdrawing groups on arene gave a slightly higher yield than those bearing electron donating groups. In general, we observed greater reactivity from benzimidates compared to the corresponding trichloroacetimidates (*e.g.* **12** *vs.* **30**, **20** *vs.* **34**). Spiro oxazoline **33** was also prepared in good yields.

Analogous to the mechanisms of the HLF reaction, we propose a mechanism featuring an intramolecular 1,5-hydrogen atom transfer (HAT) of a N radical intermediate (Scheme 5A). In this mechanism, trichloroimidate **I** first reacts with NIS to give *N*-iodoacetimidate **II**, which undergoes *N*-I homolytic cleavage under thermal conditions affording imidate N radical **III**. 1,5-HAT of **III** then gives Cβ radical **IV**. Several possible pathways might give rise to the oxazoline product **VI** from **IV**: (a) **IV** undergoes 5-endo radical cyclization to give **V**, which then gives **VI** upon SET oxidation and deprotonation;[19] (b) **IV** undergoes SET oxidation to form carbocation **VII**, which then cyclizes to give **VI**; (c) **IV** reacts with NIS or *N*-iodoacetimidate **II** to give iodinated intermediate **VIII**, which then undergoes cyclization *via* S_N2 or S_N1, generating **VI**. As shown in Scheme 5B, when 2-adamantanol substrate **37** was subjected to conditions **A**, a di-iodinated product **38** was isolated in high yields without the formation of the oxazoline product,[20] suggesting that cyclization of certain iodinated intermediates **VIII** may be challenging. Furthermore, we obtained iodinated intermediate **39** in 31% yield along with oxazoline **2** in 26% yield and unreacted **1** in 32% yield after heating **1** with NIS in DCE at



Scheme 5 Mechanistic proposal and experiments.

50 °C for 30 minutes (Scheme 5C). The cyclization of **39** to **2** proceeded quickly at 110 °C in DCE. These results provide strong evidence for pathway c in the reactions of less-sterically demanding substrates. However, pathway b *via* carbocation intermediate **VII** might operate for certain substrates, especially under reaction conditions **B**, where Ag_2O might facilitate SET oxidation of radical **IV**. This might explain the improved reaction yield of 4- to 6-membered cyclic substrates when Ag_2O is applied (see **22**, **34**, **35**).[21]

In summary, we have developed a new method for radical-mediated β-selective C(sp^3)–H amidation of *O*-alkyl trichloro- or arylimidates using NIS. This method offers a convenient and generally applicable means for C(sp^3)–H functionalization of alcohols. This amidation reaction exhibits a broad substrate scope, and proceeds with high efficiency with primary, secondary and tertiary β C(sp^3)–H bonds. This method provides a useful synthetic approach to various oxazolines and 2-amino alcohols starting from easily accessible alcohols. Mechanistic studies suggest that a HLF-type pathway through the cyclization of a Cβ-iodinated intermediate might be operative for certain substrates. However, cyclization through a β carbocation intermediate cannot be ruled out.

The authors greatly thank the Natural Science Foundation of China (21421062, 21502098, 21672105) for financial support.

Conflicts of interest

There are no conflicts to declare.

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